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TITLE: Is Homeopathy Effective for Hot Flashes and Other Estrogen-Withdrawal Symptoms in Breast Cancer Survivors? A Preliminary Randomized Controlled Trial

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**13. Abstract** ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

Background- Hot flashes, and other symptoms of estrogen withdrawal, are common in breast cancer survivors, for whom hormone replacement therapy is contraindicated. Homeopathic medicines have been used to treat menopausal symptoms for more than 100 years.
Objectives- A pilot study to determine if homeopathy may be effective in improving hot flashes and quality of life in breast cancer survivors with symptoms of estrogen withdrawal.
Methods- A randomized double-blind placebo controlled trial of 83 breast cancer survivors with at least 3 hot flashes per day for at least one month was carried out. Subjects were randomized to one of three treatment arms: a single individualized homeopathic remedy, a combination homeopathic remedy, or placebo. Number and severity of hot flashes, menopausal symptom score, general health status, and health care utilization were measured over a 12-month period.
Results/Significance- There was a positive trend towards fewer hot flashes in the group receiving the single remedy during the first three months of the study. Subjects not on tamoxifen receiving the combination remedy experienced a statistically significant increase in hot flashes. General health scores improved significantly in both homeopathy groups compared to placebo. Results of this study suggest that a larger study should be done.

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## Table of Contents

## INTRODUCTION

Hot flashes, and other symptoms of estrogen withdrawal, are common in both pre- and post-menopausal breast cancer survivors. The standard treatment for these symptoms, hormone replacement therapy, is contraindicated in breast cancer survivors due to fear that it will stimulate tumor growth. Homeopathic medicines have been used to treat hot flashes and other menopausal symptoms for more than 100 years. Our goal was to determine whether homeopathy is an effective treatment to improve the quality of life in breast cancer survivors who are experiencing hot flashes and other menopausal-type symptoms. We carried out a pilot study to demonstrate our ability to successfully conduct a full-scale trial. A randomized double-blind placebo controlled trial was carried out in a group of 83 breast cancer survivors with hot flashes and other menopausal symptoms. Subjects were randomized to one of three treatment arms: classical homeopathy, a combination homeopathic remedy, or placebo. Number and severity of hot flashes, menopausal index scores, general health status, and the use of health care services were measured over a period of 12 months.

## BODY

### Research Accomplishments

*Task 1.* Preparation for Enrollment of Patients

Letters were sent to 14 physicians at Providence Comprehensive Breast Center and affiliated clinics and 12 breast cancer support groups explaining the study and asking for patient referrals. In addition, presentations were made at Oncology Ground Rounds and to various breast cancer support groups and a booth was set up at several breast cancer survivor events. Letters were sent to potential subjects from their physicians describing the study and including a self-administered eligibility checklist. Notices were placed in breast cancer survivor newsletters with instructions to call the study coordinator for further information. Telephone screening of interested subjects was carried out by the study coordinator and potential subjects were scheduled for screening appointments.

Patient questionnaires and telephone follow-up instruments to assess outcomes were prepared and training of the study coordinator in telephone procedure was done. (Appendix 1) Data entry screens for patient intake and follow-up data collection were created and training of the study coordinator for data entry was accomplished. (Appendix 2)

*Task 2.* Enrollment of Subjects

Initial screening of potential subjects was conducted to confirm eligibility, to obtain informed consent, and to collect baseline demographic and medical information. Initial patient recruitment was slower than anticipated. We addressed this problem by expanding recruitment to potential subjects from Swedish Medical Center, which recently

acquired Providence Medical Center, the facility from which initial subjects were recruited. Presentations were given to oncologists at Swedish Medical Center, human subjects approval was obtained at that institution, and letters were sent from physicians to potential subjects. We also placed display advertisements in local newspaper asking directly for volunteers and extended the recruitment period for an additional seven months through March, 2001. These display advertisements were a more efficient means of subject recruitment, although the were also more expensive than letters from physician offices.

A total of 83 patients were recruited into the study, 79% of our projected cohort of 105 subjects. Initial homeopathic consultations and randomization of subjects to one of three treatment groups was carried out for all 83 subjects. Medicines were mailed to all subjects according to the protocol schedule. There are several reasons we believe recruitment of subjects was difficult in this study:

1. Because of the proximity of the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle, there are many trials on breast cancer survivors taking place. Thus, we were competing for subjects with several other concurrent studies.
2. The one in three chance that a woman could receive a placebo discouraged women from enrolling in a study that required participation for a period as long as one year.
3. It was difficult for women to commit for the number of follow-up visits required in this study (six over a twelve-month period).

*Task 3.* Patient Follow-up

Telephone interviews were conducted at 1, 2, 3, 6, 9, and 12 months after randomization to assess progress and to collect outcomes information. Hot flash diaries were mailed and collected for the week prior to each of these phone calls. Follow-up homeopathic consultations were conducted at 2 ,4, 6, 8, 10, and 12 months after the initial homeopathic visit. Data entry of initial consultations and follow-up visits were done as they occurred, including the information collected during the telephone interviews. Annual reports for Years I and II were submitted.

Study withdrawals were higher than anticipated, with a total of 28 withdrawals from the study. These can be summarized as follows:

| Month withdrawing | Number of participants |
|---|---|
| 1 | 7 |
| 2 | 5 |
| 3 | 3 |
| 4 | 2 |
| 6 | 5 |
| 8 | 4 |
| 10 | 2 |
| Total withdrawals | 28 |

Reasons for withdrawals were varied: 11 reported no relief from hot flashes; 4 had a cancer recurrence; 3 were advised to withdraw by their physicians because of the need for additional medications; 5 said the study was inconvenient; 1 withdrew due to a perceived adverse effect; and 4 (15%) were lost to follow-up. However, 66 of the 83 originally enrolled completed at least six months of the study. A breakdown of withdrawal of subjects by treatment group can be found in Appendix 3.

Another area of difficulty was the use of three study arms: classical homeopathy, a combination homeopathic medicine, and placebo, using a "double-dummy" design, whereby all subjects were taking two types of study medicines, one or both of which might be placebo. This was confusing to many subjects as well as to the homeopathic practitioners, who had difficulty making treatment decisions because of the uncertainty as to which treatment group a patient might have been assigned.

*Task 4.* Data Analysis and Writing of Final Reports

All data entry was completed and checked for quality control by random inspection of previously entered data. Statistical analysis of data from the study was carried out in consultation with the biostatistician, including t-tests, analysis of covariance, and effect size differences. Sample sizes that would be needed for the full-scale trial were calculated. An initial manuscripts on the results of this has been written up and is ready for submission.submission. (Appendix 3). A Powerpoint presentation of study results was created for use at professional meetings. (Appendix 4).

Future Recommendations

1. Recruitment should be more aggressive, with a larger budget that would allow for advertisements in the local media and also a stipend or gift incentive for the study participants. In addition, recruitment in areas outside of a major metropolitan area such as Seattle should be considered, since there are many ongoing studies of breast cancer survivors in this area and much competition for study subjects.
2. The study period should be shortened to no longer than six months, as it is unreasonable to expect women who are receiving a placebo to continue for one year with no improvement in their symptoms. Also, in order for a treatment to be used in the "real world" of women with hot flashes, results should be evident within a few months period of tiem.
3. Elimination of the double-dummy design, which we found difficult for both patients and practitioners. Subjects could be randomized into one of two treatment arms, single homeopathic remedy or combination, then for each of these arms subjects would again be randomized to verum or placebo. This would make treatment decisions for the homeopathic prescribers more customary to what they experience in actual practice and also allow for a more simple dosage schedule for subjects in the trial.

## KEY RESEARCH ACCOMPLISHMENTS

- Experience gained in methods of recruitment of study subjects
- Enrollment of 83 subjects and retention of 55 (66%) over a period of one year
- Study design and treatment protocol tested and weaknesses identified:
  - Study period of one year too long for recruitment and retention of subjects
  - Double-dummy design difficult for patients and homeopathic providers
  - Use of tamoxifen confounded study results
  - Dosage schedule for homeopathic combination medicine not consistent with current over-the-counter usage
- Instruments for assessing treatment outcomes tested and found adequate
- Estimates of samples sizes needed for future full-size trials as follows:
  - Using the results of the 6 month assessment of severity score in the single remedy vs placebo group: 250 subjects needed in each treatment arm for a statistical power of 80% and a power of 0.05.
- Determination of the following measurable trends toward reduction of symptoms using homeopathy:
  - Trend towards decreased hot flash severity and number in single remedy group during first three months of treatment
  - Statistically significant improvement in general health found in both homeopathy groups compared with placebo over entire study period
- Comparison of two methods of homeopathy- the classical, single remedy approach and the combination homeopathic medicine
  - Homeopathic combination found to increase number of hot flashes and headaches when compared to both single remedy and placebo in those patients not receiving tamoxifen- possibly due to homeopathic "proving" effect
  - Future studies should randomize to single or combination groups with separate placebo groups for each arm and use more appropriate dosage schedule for the combination group.

## REPORTABLE OUTCOMES

- Manuscript written for submission to professional journals (Appendix 3)
- Powerpoint presentation at the Royal London Homeopathic Hospital Conference April 3, 2003 (Appendix 4)

## CONCLUSIONS

This study suggests that homeopathic medications, both single and in combination, may be effective in improving general health in breast cancer survivors suffering from hot flashes and other menopausal symptoms. It also suggests that single remedy homeopathy is effective in reducing the number and severity of hot flashes, even in those taking tamoxifen. This treatment also could be of value to the larger population of women who are not breast cancer survivors, but who want to avoid hormone replacement due to increased risk of breast cancer and other diseases. Future studies also

should include women who are not breast cancer survivors so that more can be understood about the value of this treatment in those not taking tamoxifen or other estrogen inhibitors. Larger samples sizes should be utilized to increase statistical power and the study period should be shortened to six months.

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# APPENDIX 1- PATIENT QUESTIONNAIRES

**BASELINE QUESTIONNAIRE**

Homeopathic Treatment of Hot Flashes in Breast Cancer Survivors

ID#_____ Today's Date_____

Birth date (MM/DD/YY) _____ Occupation _____

Street Address _____

City _____ State ____ Zip Code_____

Day Phone _____ Evening Phone _____

What is the highest year in school you completed?

(1) ❑ Less than high school graduate
(2) ❑ High school graduate
(3) ❑ Attended or graduated from technical school
(4) ❑ Some College
(5) ❑ Graduated from college
(6) ❑ Completed graduate or professional degree

What race or ethnicity do you consider yourself to be?

(1) ❑ White or Caucasian
(2) ❑ Black or African American
(3) ❑ Asian or Pacific Islander
(4) ❑ Hispanic or Chicano
(5) ❑ Other: *Specify* _____

Which of the following best describes your current marital status?

(1) ❑ Married or living as married
(2) ❑ Widowed
(3) ❑ Divorced
(4) ❑ Separated
(5) ❑ Never married

Which of the following categories best describes your total annual family income, before taxes?

(1) ❑ $10,000 to $25,000
(2) ❑ $25,000 to $50,000
(3) ❑ $50,000 to $75,000
(4) ❑ $75,000 to $100,000
(5) ❑ $100,000 or More

Which of the following best describes your current employment situation?

(1) ❑ Self-employed
(2) ❑ Employed on a job for pay
(3) ❑ Extended sick leave/leave without pay.
(4) ❑ Homemaker
(5) ❑ Student
(6) ❑ Unemployed
(7) ❑ Retired
(8) ❑ Other: *Specify* _____

# BREAST CANCER MEDICAL HISTORY

**PATIENT ID #:** _____ **TODAY'S DATE:** _____

Name of Personal Physician: _____

Date of Diagnosis: _____ Laterality: _____

Stage at Diagnosis: _____ Histology: _____

Treatment:

Date of Surgery: _____ Type of Surgery: _____

Chemotherapy: ____ Yes ____ No
Date Started: _____ Date Completed: _____
1st Chemotherapy Drug _____
2nd Chemotherapy Drug _____
3rd Chemotherapy Drug _____

Radiation Therapy: ____ Yes ____ No
Date Started: _____ Date Completed: _____

Hormone Therapy: ____ Yes ____ No
Date Started: _____ Date Completed: _____

Are you currently taking Tamoxifen: ____ Yes ____ No

Do you have any other health problems for which you take regular medications?
____ Yes ____ No
If yes, please complete the following:

| Name of Health Problem | Medication Taking | How Often |
|---|---|---|
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |

Cancer status at last follow-up:
- ❑ Cancer not present
- ❑ Cancer present
- ❑ Cancer status unknown

Subgroup Type _____ FSH Level _____

# DAILY PATIENT QUESTIONNAIRE

## HOMEOPATHY FOR HOT FLASHES

**Patient ID #:** _____
**Study Month:** _____
**Date of Week Started:** ___/___/___
M D Y

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|---|
| Day/Date: | ___/___ | ___/___ | ___/___ | ___/___ | ___/___ | ___/___ | ___/___ |
| Severity: Number of Today's hot flashes that were mild, moderate, severe, or very severe? | ___mild<br>___moderate<br>___severe<br>___very severe | ___mild<br>___moderate<br>___severe<br>___very severe | ___mild<br>___moderate<br>___severe<br>___very severe | ___mild<br>___moderate<br>___severe<br>___very severe | ___mild<br>___moderate<br>___severe<br>___very severe | ___mild<br>___moderate<br>___severe<br>___very severe | ___mild<br>___moderate<br>___severe<br>___very severe |
| Total number of hot flashes today* | | | | | | | |

*One day should be considered to be 24-hour period (i.e. 7:00 a.m. or midnight to midnight).

Date week stopped: ___/___/___
M D Y

1. Are you continuing to take your study medication every day? ____yes ____no

2. How many tablets do you think you missed this week? ____

3. Is the study medication causing any side effects?

diarrhea ____no ____yes

nausea ____no ____yes

vomiting ____no ____yes

excess bloating/gas ____no ____yes

other ____no ____yes, please describe _____

4. Other comments: _____

**PATIENT INFORMATION SHEET**
(Loprinzi, 1994)

**Hot Flash Definitions for the Female Patient**

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Please refer to these examples of hot flashes that have been given by cancer survivors in previous studies when describing their hot flash severity. One or more of these descriptions may help to categorize your hot flash as mild, moderate, severe or very severe.

MILD

Duration: Lasting less than 5 minutes

Physical symptoms: Warmth, felt uncomfortable, red face

Emotional symptoms: Not expected

Action needed: Usually no action taken

MODERATE

Duration: Lasting up to 15 minutes

Physical Symptoms: Head, neck, ears, or whole body felt warm; tense, tight muscles; clammy (wet) skin; a change in heart rate or rhythm (heart speeds up or changes beat); some sweating; dry mouth

Emotional Symptoms: Felt irritated, felt agitated (restless), felt as though energy was drained out, felt embarrassed when having a hot flash in front of others, felt tired, felt annoyed

Action needed: Needed to use a fan, awakened sometimes at night, needed to uncover, took off layers of clothing, frank water, opened the windows even when cold outside, wore lighter clothing

SEVERE

Duration: Lasting up to 20 minutes

Physical symptoms: Warmth, sometimes described as a raging furnace or burning up; a change in heart rate or rhythm (heart speeds up or changes beat); felt faint; headache; severe sweating; weakness, a prickling, stinging sensation over skin; chest heaviness

Emotional symptoms: Embarrassment, anxiety, feelings of having a panic attack

Action needed: Needed to stop what was being done at that time, usually awakened at night and removed covers, needed to remove clothes, opened windows, kept the house a cooler temperature, frequently used fans

VERY SEVERE

Duration: Lasting up to 45 minutes

Physical symptoms: Boiling heat, rolling sweat, difficulty breathing, felt faint, felt dizzy, feet and/or legs cramping, a change in heart rate or rhythm (heart speeds up or changes beat), felt slightly sick to stomach

Emotional symptoms: Felt distressed, had the urge to escape, had difficulty functioning

Action needed: Awakened frequently at night, needed to change sheets and pajamas, needed to take a cold shower, needed to hold ice on skin

**Kupperman Menopausal Index Score**

Patient ID # _____ Today's Date _____ Visit Month _____

Please circle below the word that best describes the severity of the following menopausal symptoms that you experience:

| | | | | |
|---|---|---|---|---|
| Hot Flashes | None | Slight | Moderate | Severe |
| Numbness/ Tingling | None | Slight | Moderate | Severe |
| Insomnia | None | Slight | Moderate | Severe |
| Nervousness | None | Slight | Moderate | Severe |
| Depression | None | Slight | Moderate | Severe |
| Dizziness | None | Slight | Moderate | Severe |
| Fatigue | None | Slight | Moderate | Severe |
| Muscle/joint pain | None | Slight | Moderate | Severe |
| Headaches | None | Slight | Moderate | Severe |
| Palpitations | None | Slight | Moderate | Severe |
| Itching | None | Slight | Moderate | Severe |
| Vaginal Dryness | None | Slight | Moderate | Severe |
| Low Sex Drive | None | Slight | Moderate | Severe |

# The SF-36™ Health Survey

**Patient ID #:** _____ **Date:** _____ **Study Month:** _____

## Instructions for Completing the Questionnaire

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

## EXAMPLE

**This is for your review.** Do not answer this question. The questionnaire begins with the section ***Your Health in General*** below.

For each question you will be asked to fill in a bubble in each line:

1. How strongly do you agree or disagree with each of the following statements?

| | Strongly agree | Agree | Uncertain | Disagree | Strongly disagree |
|---|---|---|---|---|---|
| a) I enjoy listening to music. | ○ | ● | ○ | ○ | ○ |
| b) I enjoy reading magazines. | ● | ○ | ○ | ○ | ○ |

Please begin answering the questions now.

# Your Health in General

1. In general, would you say your health is:

| Excellent | Very good | Good | Fair | Poor |
|---|---|---|---|---|
| ○ | ○ | ○ | ○ | ○ |

2. **Compared to one year ago**, how would you rate your health in general now?

| Much better now than one year ago | Somewhat better now than one year ago | About the same as one year ago | Somewhat worse now than one year ago | Much worse now than one year ago |
|---|---|---|---|---|
| ○ | ○ | ○ | ○ | ○ |

***Please turn the page and continue.***

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3. The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

| | Yes, Limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports | ○ | ○ | ○ |
| b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | ○ | ○ | ○ |
| c) Lifting or carrying groceries | ○ | ○ | ○ |
| d) Climbing **several** flights of stairs | ○ | ○ | ○ |
| e) Climbing **one** flight of stairs | ○ | ○ | ○ |
| f) Bending, kneeling, or stooping | ○ | ○ | ○ |
| g) Walking **more than a mile** | ○ | ○ | ○ |
| h) Walking **several blocks** | ○ | ○ | ○ |
| i) Walking **one block** | ○ | ○ | ○ |
| j) Bathing or dressing yourself | ○ | ○ | ○ |

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

| | Yes | No |
|---|---|---|
| a) Cut down on the **amount of time** you spent on work or other activities | ○ | ○ |
| b) **Accomplished less** than you would like | ○ | ○ |
| c) Were limited in the **kind** of work or other activities | ○ | ○ |
| d) Had **difficulty** performing the work or other activities (for example, it took extra time) | ○ | ○ |

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

| | Yes | No |
|---|---|---|
| a) Cut down on the **amount of time** you spent on work or other activities | ○ | ○ |
| b) **Accomplished less** than you would like | ○ | ○ |
| c) Didn't do work or other activities as **carefully** as usual | ○ | ○ |

***Please turn the page to continue.***

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

| Not at all | Slightly | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ○ | ○ | ○ | ○ | ○ |

7. How much bodily pain have you had during the **past 4 weeks?**

| None | Very mild | Mild | Moderate | Severe | Very severe |
|---|---|---|---|---|---|
| ○ | ○ | ○ | ○ | ○ | ○ |

8. During the **past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

| Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ○ | ○ | ○ | ○ | ○ |

9. These questions are about how you feel and how things have been with you during the **past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**...

| | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| a) did you feel full of pep? | ○ | ○ | ○ | ○ | ○ | ○ |
| b) have you been a very nervous person? | ○ | ○ | ○ | ○ | ○ | ○ |
| c) have you felt so down in the dumps nothing could cheer you up? | ○ | ○ | ○ | ○ | ○ | ○ |
| d) have you felt calm and peaceful? | ○ | ○ | ○ | ○ | ○ | ○ |
| e) did you have a lot of energy? | ○ | ○ | ○ | ○ | ○ | ○ |
| f) have you felt downhearted and blue? | ○ | ○ | ○ | ○ | ○ | ○ |
| g) did you feel worn out? | ○ | ○ | ○ | ○ | ○ | ○ |
| h) have you been a happy person? | ○ | ○ | ○ | ○ | ○ | ○ |
| i) did you feel tired? | ○ | ○ | ○ | ○ | ○ | ○ |

10. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|
| ○ | ○ | ○ | ○ | ○ |

11. How TRUE or FALSE is each of the following statements for you?

| | Definitely true | Mostly true | Don't know | Mostly false | Definitely false |
|---|---|---|---|---|---|
| a) I seem to get sick a little easier than other people | ○ | ○ | ○ | ○ | ○ |
| b) I am as healthy as anybody I know | ○ | ○ | ○ | ○ | ○ |
| c) I expect my health to get worse | ○ | ○ | ○ | ○ | ○ |
| d) My health is excellent | ○ | ○ | ○ | ○ | ○ |

***THANK YOU* FOR COMPLETING THIS QUESTIONNAIRE!**

**IS HOMEOPATHY EFFECTIVE FOR THE TREATMENT OF HOT FLASHES AND OTHER MENOPAUSAL TYPE SYMPTOMS?**

Here are some questions about your participation in the study. In terms of your satisfaction, how would you rate each of the following?

Part I:

| | Excellent | Very Good | Good | Fair | Poor |
|---|---|---|---|---|---|
| 1. How long you waited to get an appointment | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. Convenience and location of office | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. Getting through to study personnel by phone | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. Length of time waiting at the office | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. Time spent with the person you saw | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. Explanation of what was done for you | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. The technical skills (thoroughness, carefulness, competence) of the person you saw. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. The personal manner (courtesy, respect, sensitivity, friendliness) of the person you saw | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. Your experience overall | ☐ | ☐ | ☐ | ☐ | ☐ |

Part II

1. Why did you decide to join the study?

2. Do you have any suggestions about how to make the study better?

3. Did you have any prior experience with alternative medicine before joining the study? If so, please describe.

Part III

4. Have you visited another doctor/clinic/ or hospital during the past 3 months for routine or emergency care? ____Yes _____No
If yes, list the following:

| Date | Name of doctor/clinic | Purpose of visit(s) |
|---|---|---|

5. Have you stopped or decreased the dosage of any of your ongoing medications during the last three months?

_____Yes _____No If yes, list the following:

| Date | Name of medication | Action taken (stopped/decreased) | Condition being treated |
|---|---|---|---|

6. Have you added any new medications or increased the dosage of any of your ongoing medications during the past three months? If yes, list the following:

| Date | Name of medication | Action taken (added/increased) | Condition being treated |
|---|---|---|---|

7. Have you taken any other medications during the past 3 months for a temporary condition (i.e., antibiotics for infection, etc)? If yes, list the following

| Date | Name of medication | Duration of treatment | Condition being treated |
|---|---|---|---|

THANK YOU FOR YOUR COOPERATION IN PARTICIPATING IN THIS STUDY

Case # BC-_____ Date _____ Visit # _____
mm/dd/yy

Evaluation of previous prescription (most recent remedy given) (circle one):

1= Curative
2= Possible Curative
3= Unsure
4= Incorrect Remedy
5= Antidote What kind? _____
6= Relapse

Did an aggravation occur? Yes No

Today's prescription: (If none or placebo, write that in as Remedy)

Remedy _____ Potency _____ Frequency_____

Confidence in today's prescription: (circle one)

1= Excellent
2= Good
3= Fair
4= Poor

Type of prescription (circle one or more):

1= Essence
2= Totality
3= Keynote
4= Other _____

Key rubrics (if any):

Comments:

What treatment group do you think this patient is in?

1= Active classical homeopathy
2= Active combination remedy
3= Placebo
4= Don't know

Prescriber's name_____

# TELEPHONE INTERVIEW QUESTIONNAIRE

1. Have you had any problems taking your daily medication? ☐ Yes ☐ No If yes, please describe: _____

2. In the past month, on average, how often have you been taking the "daily" medication?
☐ 2-3 x daily ☐ 1 x daily ☐ several times/week ☐ weekly ☐ less than weekly
☐ Other - Describe: _____

3. Does the study medication appear to be causing any side effects? ☐ Yes ☐ No If yes, please describe: _____

4. Have you been drinking coffee or using anything else that might counteract the homeopathic medication? ☐ Yes ☐ No If yes, please describe: _____

5. Have you had any new medical problems since your last appointment/phone call?
☐ Yes ☐ No If yes, please describe: _____

6. Have you taken any prescription or non-prescription medication since your last appointment/phone call? ☐ Yes ☐ No If yes, please describe: _____

7. Have you used any other types of alternative or non-alternative medical treatment?
☐ Yes ☐ No If yes, please describe: _____

8. Is there anything else that has happened since your last appointment/phone call that you think might be important? ☐ Yes ☐ No If yes, please describe: _____

# APPENDIX 2- DATA ENTRY SCREENS

BREAST CANCER MEDICAL HISTORY

PT ID BC-### SCREENING DATE <MM/DD/YY>

NAME OF PERSONAL {PHYSICIAN} _____

DATE OF {DIAGNOSIS} <MM/DD/YY>

AJCC {STAGE} AT DIAGNOSIS <A >

LATERALITY <A> HISTOLOGY <A >

TREATMENT:

DATE OF SURGERY <MM/DD/YY>

TYPE OF SURGERY #
1=Lumpectomy
2=Lumpectomy and LN Dissection
3=Partial Mastectomy
4=Partial Mastectomy and LN Dissection
5=Simple Mastectomy
6=Modified Radical Mastectomy

CHEMO <Y> {CHEM START} DATE <MM/DD/YY> {CHEM STOP} DATE <MM/DD/YY>

DRUG 1 <A >
DRUG 2 <A >
DRUG 3 <A >

RADIATION <Y> {RAD START} DATE <MM/DD/YY> {RAD STOP} DATE <MM/DD/YY>

HORMONE <Y> {HORM START} DATE <MM/DD/YY> {HORM STOP} DATE <MM/DD/YY>

ARE YOU CURRENTLY TAKING {TAMOXIFEN}? <Y>

DO YOU HAVE ANY OTHER HEALTH PROBLEMS FOR WHICH YOU TAKE REGULAR MEDICATIONS? <Y> IF YES, PLEASE COMPLETE THE FOLLOWING ABOUT THE MEDICATIONS YOU ARE TAKING:

NAME OF HEALTH {PROBLEM1} _____
{MEDICATION1} TAKING _____
HOW {OFTEN1} _____

NAME OF HEALTH {PROBLEM2} _____
{MEDICATION2} TAKING _____
HOW {OFTEN2} _____

NAME OF HEALTH {PROBLEM3} _____
{MEDICATION3} TAKING _____
HOW {OFTEN3} _____

NAME OF HEALTH {PROBLEM4} _____
{MEDICATION4} TAKING _____
HOW {OFTEN4} _____

CANCER STATUS AT LAST FOLLOW-UP: #
1=NO CANCER PRESENT
2=CANCER PRESENT
3=CANCER STATUS UNKNOWN

SUBGROUP TYPE <A>

FSH LEVEL ###.#

Patient ID BC-### Today's Date <mm/dd/yy>

Birthdate <mm/dd/yy>

OCCUPATION _____

ADDRESS _____

_____

CITY _____

STATE __

ZIP CODE #####-####

DAY PHONE <LONG DISTANCE>

EVE PHONE <LONG DISTANCE>

LAST YR EDU: #
1=LESS THAN HIGH SCHOOL
2=HIGH SCHOOL GRADUATE
3=ATTENDED OR GRADUATED TECHNICAL SCHOOL
4=SOME COLLEGE
5=GRADUATED COLLEGE
6=GRADUATE OR PROFESSIONAL DEGREE

RACE/ETHN: #
1=WHITE OR CAUCASION
2=BLACK OR AFRICAN AMERICAN
3=ASIAN OR PACIFIC ISLANDER
4=HISPANIC
5=OTHER: SPECIFY _____

MARITAL STATUS: #
1=MARRIED OR LIVING AS MARRIED
2=WIDOWED
3=DIVORCED
4=SEPARATED
5=NEVER MARRIED

INCOME: #
1=$10,000 TO $25,000
2=$25,000 TO $50,000
3=$50,000 TO $75,000
4=$75,000 TO $100,000
5=$100,000 OR MORE

EMPL STATUS: #
1=SELF-EMPLOYED
2=EMPLOYED ON A JOB FOR PAY
3=EXTENDED SICK LEAVE/LEAVE WITHOUT PAY
4=HOMEMAKER
5=STUDENT
6=UNEMPLOYED
7=RETIRED
8=OTHER: SPECIFY _____

REFERRAL SOURCE: _____

GROUP: <A>

# HOT FLASH DAILY PATIENT QUESTIONNAIRE

PT ID BC-###  DATE {STARTED} <MM/DD/YY>  STUDY MONTH ##-<A>

EACH DAY WRITE THE TOTAL NUMBER OF HOT FLASHES YOU EXPERIENCED AND HOW SEVERE EACH HOT FLASH WAS:

DAY 1
## MILD
## MODERATE
## SEVERE
## VERY SEVERE
## TOTAL

DAY 2
## MILD
## MODERATE
## SEVERE
## VERY SEVERE
## TOTAL

DAY 3
## MILD
## MODERATE
## SEVERE
## VERY SEVERE
## TOTAL

DAY 4
## MILD
## MODERATE
## SEVERE
## VERY SEVERE
## TOTAL

DAY 5
## MILD
## MODERATE
## SEVERE
## VERY SEVERE
## TOTAL

DAY 6
## MILD
## MODERATE
## SEVERE
## VERY SEVERE
## TOTAL

DAY 7
## MILD
## MODERATE
## SEVERE
## VERY SEVERE
## TOTAL

DATE {STOPPED}: <MM/DD/YY>

1. ARE YOU {CONTINUING} TO TAKE YOUR MEDICATIONS EVERY DAY? <Y>

2. HOW MANY TABLETS DO YOU THINK YOU {MISSED} THIS WEEK? #

3. IS THE STUDY MEDICATION CAUSING ANY {SIDE EFFECTS}?

DIARRHEA <Y>
NAUSEA <Y>
VOMITING <Y>
EXCESS BLOATING/GAS <Y>
OTHER <Y>. IF YES, DESCRIBE _____
_____

# KUPPERMAN MENOPAUSAL INDEX SCORE

PT ID BC-###  TODAY'S DATE <MM/DD/YY>  STUDY MONTH ##

WHICH WORD BEST DESCRIBES THE SEVERITY OF THE FOLLOWING MENOPAUSAL SYMPTOMS THAT YOU EXPERIENCE:

1=NONE
2=SLIGHT
3=MODERATE
4=SEVERE

HOT FLASHES #

NUMBNESS/TINGLING #

INSOMNIA #

NERVOUSNESS #

DEPRESSION #

DIZZINESS #

FATIGUE #

MUSCLE/JOINT PAIN #

HEADACHES #

PALPATIONS #

ITCHING #

VAGINAL DRYNESS #

LOW SEX DRIVE #

TOTAL SCORE ##

HEALTH STATUS QUESTIONNAIRE

~~PATIENT~~ PT ID: BC-###  DATE: <MM/DD/YY>  STUDY MONTH ##

1. IN {GENERAL}, WOULD YOU SAY YOUR HEALTH IS: #
   1=EXCELLENT
   2=VERY GOOD
   3=GOOD
   4=FAIR
   5=POOR

2. COMPARED TO {ONE YEAR AGO}, HOW WOULD YOU RATE YOUR HEALTH IN GENERAL NOW? #
   1=MUCH BETTER NOW THAN ONE YEAR AGO
   2=SOMEWHAT BETTER NOW THAN ONE YEAR AGO
   3=ABOUT THE SAME
   4=SOMEWHAT WORSE NOW THAN ONE YEAR AGO
   5=MUCH WORSE NOW THAN ONE YEAR AGO

3. DOES YOUR HEALTH {LIMIT} YOUR DAILY ACTIVITIES?
   1=YES, LIMITED A LOT
   2=YES, LIMITED A LITTLE
   3=NO, NOT LIMITED AT ALL

A. # VIGOROUS ACTIVITIES=RUNNING, LIFTING HEAVY OBJECTS, PARTICIPATING IN STRENUOUS SPORTS
B. # MODERATE ACTIVITIES=MOVING A TABLE, PUSHING A VACUUM CLEANER, BOWLING OR PLAYING GOLF
C. # LIFTING OR CARRYING GROCERIES
D. # CLIMBING SEVERAL FLIGHTS OF STAIRS
E. # CLIMBING ONE FLIGHT OF STAIRS
F. # BENDING, KNEELING, OR STOOPING
G. # WALKING MORE THAN A MILE
H. # WALKING SEVERAL BLOCKS
I. # WALKING ONE BLOCK
J. # BATHING AND DRESSING YOURSELF

4. DURING THE PAST 4 WEEKS, HAVE YOU HAD ANY OF THE FOLOWING PROBLEMS WITH YOUR WORK OR OTHER REGULAR DAILY ACTIVITIES AS A RESULT OF YOUR {PHYSICAL} HEALTH?

A. <Y> CUT DOWN ON THE AMOUNT OF TIME YOU SPENT ON WORK OR OTHER ACTIVITIES
B. <Y> ACCOMPLISHED LESS THAN YOU WOULD LIKE
C. <Y> WERE LIMITED IN THE KIND OF WORK OR OTHER ACTIVITIES
D. <Y> HAD DIFFICULTY PERFORMING THE WORK OR OTHER ACTIVITIES (EXTRA EFFORT
)

5. DURING THE PAST 4 WEEKS HAVE YOU HAD ANY OF THE FOLLOWING PROBLEMS WITH YOUR WORK OR OTHER REGULAR DAILY ACTIVITIES AS A RESULT OF ANY {EMOTIONA
L}

   PROBLEMS (SUCH AS FEELING DEPRESSED OR ANXIOUS)?

A. <Y> CUT DOWN ON THE AMOUNT OF TIME YOU SPENT ON WORK OR OTHER ACTIVITIES
B. <Y> ACCOMPLISHED LESS THAN YOU WOULD LIKE
C. <Y> DIDN'T DO WORK OR OTHER ACTIVITIES AS CAREFULLY AS USUAL

6. DURING THE PAST 4 WEEKS, TO WHAT EXTENT HAS YOUR PHYSICAL HEALTH OR EMOTIONAL PROBLEMS {INTERFERED} WITH YOUR NORMAL SOCIAL ACTIVITIES WITH FAMILY, FRIENDS, NEIGHBORS, OR GROUPS? #
   1=NOT AT ALL
   2=SLIGHTLY
   3=MODERATELY
   4=QUITE A BIT
   5=EXTREMELY

1=NONE
2=VERY MILD
3=MILD
4=MODERATE
5=SEVERE
6=VERY SEVERE

8. DURING THE PAST 4 WEEKS, HOW MUCH DID {PAIN INTERFERE} WITH YOUR NORMAL WORK (INCLUDING WORK BOTH OUTSIDE THE HOME AND HOUSEWORK)? #
1=NOT AT ALL
2=A LITTLE BIT
3=MODERATELY
4=QUITE A BIT
5=EXTREMELY

{FEELINGS}: THESE QUESTIONS ARE ABOUT HOW YOU FEEL AND HOW THINGS HAVE BEEN WITH YOU DURING THE PAST MONTH.
1=ALL OF THE TIME
2=MOST OF THE TIME
3=A GOOD BIT OF THE TIME
4=SOME OF THE TIME
5=A LITTLE OF THE TIME
6=NONE OF THE TIME

HOW MUCH OF THE TIME DURING THE PAST MONTH...
A. DID YOU FEEL FULL OF PEP? #
B. HAVE YOU BEEN A VERY NERVOUS PERSON? #
C. HAVE YOU FELT SO DOWN IN THE DUMPS NOTHING COULD CHEER YOU UP? #
D. HAVE YOU FELT CALM AND PEACEFUL? #
E. DID YOU HAVE A LOT OF ENERGY? #
F. HAVE YOU FELT DOWNHEARTED AND BLUE? #
G. DID YOU FEEL WORN OUT? #
H. HAVE YOU BEEN A HAPPY PERSON? #
I. DID YOU FEEL TIRED? #
J. HAS YOUR HEALTH LIMITED YOUR SOCIAL ACTIVITIES (VISITING FRIENDS/RELATIVES)? #

{HEALTH} IN GENERAL: 1=DEFINITELY TRUE
2=MOSTLY TRUE
3=NOT SURE
4=MOSTLY FALSE
5=DEFINITELY FALSE

A. I SEEM TO GET SICK A LITTLE EASIER THAN OTHER PEOPLE. #
B. I AM AS HEALTHY AS ANYBODY I KNOW. #
C. I EXPECT MY HEALTH TO GET WORSE. #
D. MY HEALTH IS EXCELLENT. #

PATIENT SATISFACTION QUESTIONNAIRE

PATIENT ID BC-###  DATE: <MM/DD/YY>  STUDY MONTH ##

PART I:

HERE ARE SOME QUESTIONS ABOUT YOUR PARTICIPATOIN IN THE STUDY. IN TERMS OF YOUR SATISFACTION, HOW WOULD YOU RATE EACH OF THE FOLLOWING:

1=EXCELLENT
2=VERY GOOD
3=GOOD
4=FAIR
5=POOR

A. HOW LONG YOU WAITED TO GET AN APPOINTMENT #
B. CONVENIENCE AND LOCATION OF OFFICE #
C. GETTING THROUGH TO STUDY PERSONNEL BY PHONE #
D. LENGTH OF TIME WAITING AT THE OFFICE #
E. TIME SPENT WITH THE PERSON YOU SAW #
F. EXPLANATION OF WHAT WAS DONE FOR YOU #
G. THE TECHNICAL SKILLS (THOROUGHNESS, CAREFULNESS, COMPETENCE) OF THE PERSON YOU SAW #
H. THE PERSONAL MANNER (COURTESY, RESPECT, SENSITIVITY, FRIENDLINESS) OF THE PERSON YOU SAW #
I. YOUR EXPERIENCE OVERALL #

PART II:

1. {WHY} DID YOU DECIDE TO JOIN THE STUDY?

_____
_____
_____

2. DO YOU HAVE ANY {SUGGESTIONS} ABOUT HOW TO MAKE THE STUDY BETTER?

_____
_____
_____

3. DID YOU HAVE ANY {PRIOR EXPERIENCE} WITH ALTERNATIVE MEDICINE BEFORE JOINING THE STUDY? <Y> IF SO, PLEASE DESCRIBE:

_____
_____
_____

PART III:

4. HAVE YOU {VISITED} ANOTHER DOCTOR/CLINIC/OR HOSPITAL DURING THE PAST 3 MONTHS FOR ROUTINE OR EMERGENCY CARE? <Y>
   DATE <MM/DD/YY>
   NAME OF DOCTOR/CLINIC: _____
   PURPOSE OF VISIT: _____

5. HAVE YOU {STOPPED} OR DECREASED THE DOSAGE OF ANY OF YOUR ONGOING MEDICATIONS DURING THE LAST THREE MONTHS? <Y> IF YES, LIST THE FOLLOWING

   DATE <MM/DD/YY>
   NAME OF MEDICATION: _____
   ACTION TAKEN (STOPPED/DECREASED): _____
   CONDITION BEING TREATED: _____

6. HAVE YOU {ADDED} ANY NEW MEDICATIONS OR INCREASED THE DOSAGE OF ANY OF YOUR

DATE <MM/DD/YY>
NAME OF MEDICATION: _____
ACTION TAKEN (ADDED/INCREASED): _____
CONDITION BEING TREATED: _____

7. HAVE YOU TAKEN ANY OTHER MEDICATIONS DURING THE PAST 3 MONTHS FOR A {TEMPORARY}
CONDITION (I.E., ANTIBIOTICS FOR INFECTION, ETC)? <Y> IF YES, LIST THE FOLLOWING:
DATE <MM/DD/YY>
NAME OF MEDICATION: _____
DURATION OF TREATMENT: _____
CONDITION BEING TREATED: _____

CASE # BC-###  DATE <MM/DD/YY>  VISIT ###

EVALUATION OF PREVIOUS PRESCRIPTION (MOST RECENT REMEDY GIVEN) #
1=CURATIVE
2=POSSIBLE CURATIVE
3=UNSURE
4=INCORRECT REMEDY
5=ANTIDOTE
6=RELAPSE

WHAT {KIND ANTIDOTE} _____

DID AN AGGRAVATION OCCUR? <Y>

TODAY'S PRESCRIPTION: (IF NONE OR PLACEBO, WRITE THAT IN AS REMEDY)

REMEDY <A  >

POTENCY #
1=30C
2=200C
3=1M
4=10M
5=LM
6=OTHER

FREQUENCY #
1=SINGLE
2=WEEKLY
3=EVERY OTHER WEEK
4=MONTHLY

CONFIDENCE IN TODAY'S PRESCRIPTION: #
1=EXCELLENT
2=GOOD
3=FAIR
4=POOR

TYPE OF PRESCRIPTION: #
1=ESSENCE
2=TOTALITY
3=KEYNOTE
4=OTHER _____

KEY RUBRICS (IF ANY): _____
_____
_____
_____
_____

COMMENTS: _____
_____
_____

WHAT TREATMENT GROUP DO YOU THINK THIS PATIENT IS IN? #
1=ACTIVE CLASSICAL HOMEOPATHY
2=ACTIVE COMBINATION REMEDY
3=PLACEBO
4=DON'T KNOW

PRESCRIBER'S NAME: #
1=CASTRO
2=GOLDMAN
3=HERON
4=VAUGHTERS
5=OTHER

PHONE INTERVIEW QUESTIONNAIRE:

PT ID BC-### TODAY'S DATE <MM/DD/YY> STUDY MONTH ##

1. Have you had any {problems} taking your medication? <Y>
   If yes, describe: _____
   _____
   _____

2. In the past month, on average, how often have you been taking the {"daily"} medication? <A>
   a = 2-3 x daily
   b = 1 x daily
   c = several times/week
   d = weekly
   e = less than weekly
   f = Other Describe: _____
   _____
   _____

3. Does the study medication appear to be causing any {side effects}? <Y> If yes, describe: _____
   _____
   _____

4. Have you been drinking coffee or using anything else that might {counteract} the homeopathic medication? <Y>
   If yes, describe: _____
   _____
   _____

5. Have you had any new {med problems} since your last appointment/phone call? <Y> If yes, describe: _____
   _____
   _____

6. Have you taken any {prescription} or non-prescription medication since your last appointment/pnone call? <Y>
   If yes, describe: _____
   _____
   _____

7. Have you used any other {med treatment}: alternative or non-alternative? <Y> If yes, describe: _____
   _____
   _____

8. Is there anything else that has {happened} since your last appointment/phone call that you think might be important? <Y> If yes, describe: _____
   _____
   _____

## APPENDIX 3

Is Homeopathy Effective for Hot Flashes and Other Estrogen-Withdrawal Symptoms in Breast Cancer Survivors? A Preliminary Randomized Controlled Trial

### INTRODUCTION

Hot flashes, and other symptoms of estrogen withdrawal, are common in both pre- and post-menopausal breast cancer survivors. In post-menopausal women, these symptoms are due largely to decreased ovarian function. In one study, 65% of post-menopausal breast cancer survivors experienced hot flashes, 46% complained of vaginal dryness, 44% had difficulty sleeping, and 44% reported feeling depressed. (Couzi, 1995) In addition, more than 50% of women receiving tamoxifen, both pre- and post-menopausal, complain of hot flashes, (Fisher, 1989) and women treated with chemotherapy have been found to experience significant weight changes, mood swings, hot flashes, vaginal dryness, and difficulty in sexual functioning. (Young-McCaughan, 1996)

The standard treatment for menopausal symptoms, hormone replacement therapy (HRT), is contraindicated in breast cancer survivors due to fear that it will stimulate tumor growth. (Loprinzi, 1994) Findings of increased health risks from the use of HRT in healthy post-menopausal women makes the task of finding alternative treatments for these symptoms even more important. (WGWHI 2002) Studies of non-hormonal treatments for climacteric symptoms have been largely disappointing. A study of Vitamin E showed only marginal clinical reduction of hot flashes, (Barton, 1998) soy protein was found to reduce the frequency of hot flashes, but gastrointestinal side effects were common, (Albertazzi, 1998) and clonidine was found to reduce hot flashes, but side effects were quite frequent. (Goldberg, 1994) Promising results have been found using megestrol acetate, a progestational agent, (Loprinzi, 1994) but concerns remain about its safety in breast cancer survivors. (Barton, 1998) A recent review of the complementary and alternative medicine (CAM) literature concluded that black cohosh and foods containing phytoestrogens show promise for treating menopausal symptoms, but trials failed to support the use of other CAM therapies such as dong quai, evening primrose oil, vitamin E, and acupuncture. (Kronenberg 2002).

Homeopathy was first developed in Germany by Samuel Hahnemann in the late 18th century and today is practiced widely around the world. In some European countries, as many as 30-40% of patients and physicians use homeopathy. (Ernst, 1996) In the US, it is estimated that 3.4% of the population used homeopathy in 1997, a five fold increase since 1990. (Eisenberg, 1993, Esienberg, 1997. It has been estimated that 2500 medical professionals in the U.S. currently use homeopathy to some extent in their practices. (Swander, 1994)

Homeopathy is based on the principle of similars, whereby highly dilute preparations of substances that have been found to cause symptoms in healthy volunteers are used to treat patients who have similar symptoms when ill. (Jonas, 1996) Homeopathic medicines are prepared by a process of serial dilution and shaking, according to standardized methods as specified by the Homeopathic Pharmacopoeia of the United States (HPUS), which was mandated to regulate the manufacture of homeopathic medicines as part of the Food, Drug, and Cosmetics Act of 1939. The mechanism of action of homeopathy is not well understood, but is thought to

be due to enhancement of the immune response and other auto-regulatory systems of the body. (Bellavite, 1995)

There are two main approaches to homeopathic prescribing used today in the US. *Classical homeopathy,* used widely by medical practitioners for acute and chronic illnesses, involves a 60-90 minute initial consultation. A single homeopathic medicine is prescribed, matching the specific signs and symptoms in that patient with those known to be associated with a particular medicine in the homeopathic literature. Using this individualized approach, two or more people with the same diagnosis may be given different medicines, depending on their specific symptoms. *Combination homeopathic remedies* are commonly used in over-the-counter preparations that are available to the general public for treatment of acute, self-limited conditions. These preparations consist of several different medicines known to be useful for a particular symptom or illness that are combined together into one pill.

Homeopathic medicines have been used to treat women with hot flashes and other menopausal symptoms for nearly than 150 years. (Guernsey, 1866) The homeopathic repertory, a reference book that lists the most common medicines indicated for specific symptoms, contains 41 homeopathic remedies under the category "Heat, flushes of, menopause, during" and 101 remedies under the category "menopause, during." (Schroyens, 1996). There have been two previous studies done to evaluate the use of homeopathy for menopausal symptoms. (Gauthier, 1983, Bekkering, 1993). Both found an improvement with homeopathy, but the number of patients was small and no statistically significant differences were found when compared to placebo.

Because homeopathy is a system that treats the whole person, taking into account physical, emotional, and mental symptoms, it could be of particular value to women suffering from the myriad symptoms associated with estrogen withdrawal. Studies have shown that more than half of all cancer patients use some form of alternative treatment. (Brigdon) Finding a low-cost and safe treatment for this problem would be of great benefit in improving the quality of life for breast cancer survivors.

## MATERIALS AND METHODS

### Participants

Eligibility: Patients entered into the study had a history of carcinoma in situ or Stage 1-3 breast cancer and had completed all surgical interventions, chemotherapy, and radiation treatment prior to enrollment in the study. Patients taking tamoxifen were included. Subjects had a history of hot flashes for at least one month, with an average of at least 3 hot flashes per day in the week prior to beginning treatment.

Exclusions: Patients taking any other medications specifically for the treatment of hot flashes and other associated symptoms, including specific vitamin regimens, herbs, estrogen or progestational agents, anti-depressants, or sleep medications, were excluded from the study. Patients with concurrent chronic health problems such as rheumatoid arthritis, asthma, heart disease, and inflammatory bowel disease necessitating treatment with corticosteroids were also excluded. Subjects who were expected to receive additional chemotherapy or radiation treatment within the next year were excluded, as were women who were pregnant or planned to become pregnant in the next year. Women with childbearing potential were asked to use appropriate non-hormonal birth control methods to prevent pregnancy during the trial.

Recruitment: Subjects were recruited from the Comprehensive Breast Center at Providence Hospital in Seattle and a network of affiliated neighborhood clinics, as well as Swedish Medical Center of Seattle. Enrollment took place through letters to patients from their physicians, contact with breast cancer survivor support groups, and direct advertisements in local newspapers. All interested candidates attended a screening appointment, during which eligibility was confirmed and informed consent obtained using a consent form approved by the University of Washington Human Subjects Committee, the Human Subjects Research Review Board of the Department of Defense, and the IRB of Providence Medical Center.

Intervention and randomization

At the initial visit, a homeopathic practitioner conducted a homeopathic evaluation of each subject and prescribed an individualized homeopathic medication that best matched the symptom picture for that subject. All homeopathic practitioners had at least ten years experience in classical homeopathy and were certified by one of the national homeopathic certification boards. The number of homeopathic medicines available was not limited, nor was the potency or frequency of the dose prescribed. Practitioners were asked to rate their confidence in each prescription as excellent, good, fair, or poor.

The homeopathic prescription was communicated by fax or e-mail to a homeopathic pharmacist, who randomized the subjects to one of three treatment groups: 1) a placebo combination medicine and a verum single remedy; 2) a verum combination medicine and a placebo single remedy; or 3) two placebo medications. The medications were express mailed to subjects' home addresses, along with dosage instructions. All study medications were donated by the Standard Homeopathic Company, Los Angeles, California, were identical in taste, appearance, and odor, and were dispensed in identical containers. Patients were instructed to take the combination medicine (verum or placebo) one tablet three times daily. The instructions for the single medicine were individualized and most often were given monthly or every two months.

The combination medicine was *Hyland's Menopause*, which has been sold over-the-counter in the U.S. for the treatment of hot flashes for more than 50 years. It contained the following three homeopathic medicines: *Amyl nitrate* 3X ( 1:1000 dilution), *Sanguinaria canadensis*, the Bloodroot plant, 3X (1:1000 dilution), and *Lachesis*, the poison of the Bushmaster snake, 12X (1:1,000,000,000,000 dilution). Randomization was done using computer generated random numbers in blocks of 4 and 6 and was known only to the homeopathic pharmacist. Stratification was done by age (< or > 50 years), breast cancer staging, and use of tamoxifen. None of the homeopathic practitioners, study personnel, or co-investigators knew which subjects had been randomized to which group. The code was not broken until after initial data analysis was completed (triple-blind).

Follow-up

Follow-up visits with the homeopathic practitioners were conducted at 2, 4, 6, 8, 10, and 12 months following the initial consultation. At each of these visits, the patients were evaluated, adverse side effects inquired about, and the individualized homeopathic prescription renewed or revised. Although the specific homeopathic prescription might change, subjects randomized to each group continued to receive placebo or active medicines throughout the study. Subjects were asked to bring in any remaining medication at each visit to permit an evaluation of compliance.

The subjects were interviewed by the study coordinator by telephone at 1, 2, 3, 6, 9, and 12 months after randomization to evaluate outcomes. Patients were mailed a one-week daily hot flash diary to be completed during the week prior to each of these phone calls. Any new or recurring medical problem that occurred during the course of the study was evaluated by the patient's primary physician and records of all medical visits during the study period were obtained by study personnel at the end of the study.

Outcome measures and data analysis

The primary outcome measure was the hot-flash severity score (frequency x severity), as measured by the symptom diaries at entry into the study and after 1, 2, 3, 6, 9, and 12 months of treatment. Other outcomes included the total number of hot flashes, the Kupperman Menopausal Index, an 11 symptom weighted score (Kupperman, 1953), and the SF-36 Quality of Life Score, which evaluated mental and physical health status. (Ware, 1992). Information about utilization and cost of health care during the study was also collected using chart review. The FSH level before and after treatment was measured and compared between the three groups. The chi-square statistic was used to compare discrete descriptive characteristics between groups at entry into the study and ANOVA was used to compare continuous variables.

All outcome variables could be considered as continuous, and linear regression was used to determine the association between treatments and outcomes, controlling for other covariates as needed. Generalized estimating equations (GEE) was used to accommodate the multiple observations per person. After initial analyses, it was obvious that some of the treatment effects differed between the group receiving Tamoxifen and the group not receiving Tamoxifen treatment. Thus, analyses were carried out separately for the Tamoxifen and no-Tamoxifen groups. The three-level treatment variable (single, combination, placebo) was represented by dummy variables in the analysis. For any given analysis (such as no Tamoxifen) all treatments were included in the analysis, and the difference in the mean outcome between any pair of treatments and the standard error of the difference and its statistical significance determined as the coefficient, standard error and p-value of a treatment dummy variable with an appropriately specified reference category.

In order to adjust for a "drop-out" effect, two "drop-out" variables were tried: 1) the time in months from baseline to the last observed follow-up assessment, and, 2) a dummy variable representing completion of the last follow-up at 12 months vs. an earlier drop-out. The more continuos drop-out variable (#1) was more significant in predicting outcomes and was retained for all final analyses. The baseline value of a particular outcome variable was usually highly significantly predictive of the subsequent outcome values for the variable. Thus, the repeated measurements for GEE linear regression consisted of all post-baseline assessments with the baseline value as an independent variable.

The effect of time since baseline was usually significant and substantial, and the time variable was included in all analyses. Initially, time was represented by a categorical variable (with dummy variables indicating each assessment time), but subsequent analyses showed that the categorical time variable added little in prediction to a continuous linear time variable, which was then used in all subsequent analyses. Interactions between time and treatment were tested for inclusion in multivariate models. Among 18 models tested (six outcomes for each of three patient groupings: Tamoxifen, no Tamoxifen, and all patients) only one time*treatment

interaction was significant ($p = 0.02$), but this was considered likely due to chance, given the number of analyses, and this interaction was not included in the final multivariate models.

Univariate models for the effect of treatment or other independent variables on the outcome variables always included the baseline value of each outcome variable and continuous time. The univariate analyses for the entire group of patients included, in addition, a dummy variable indicating Tamoxifen vs. no Tamoxifen treatment. Multivariate models for outcomes always included treatment and any other variables that were statistically significant for any outcome. These independent variables for multivariate analysis were, then, treatment, baseline value of the outcome variable, continuous time, age, time of dropout, and , for the analysis of the entire group of patients, the Tamoxifen dummy variable (yes/no). Residuals were examined for outliers, skewness and other data problems, but no observations had to be dropped.

## RESULTS

### Recruitment and descriptive characteristics

Recruitment of subjects took place between December 1, 1999 and March 31, 2001. Recruitment was more difficult than anticipated due to the long treatment period (one year) and the one in three chance that a woman would receive placebo. Eighty-three patients completed the initial homeopathic visit and were randomized into one of the three treatment groups. Of these, there were a total of 28 withdrawals (33.7 %), including 11 who reported no relief from hot flashes, 7 who had a cancer recurrence or withdraw due to other illness, 5 who said the study was too inconvenient, and 4 who were lost to follow-up. One patient withdrew from the study because she felt the study medication was causing diarrhea. However, 66 of the 83 originally randomized completed at least six months of the study (80.5%). (Table 1) There were half as many withdrawals in the single remedy group compared to the combination and placebo groups at six and 12 months, although this was not statistically significant.

There were no significant differences in demographic factors or previous history of breast cancer staging or treatments between the three groups. (Table 2) Comparison of these factors between the subjects who withdrew from the study and those who completed the full 12 months also failed to find any significant differences. Nearly sixty percent of women in the study were taking tamoxifen. There were also no significant differences between the three groups in number of hot flashes, Kupperman Menopausal Index (KMI), and quality of life indices at entry into the study.

### Homeopathic remedies

There were 35 different single remedies prescribed at the first visit, the most common of which were Sepia (9), Calcarea carbonica (8), Sulphur (6), Lachesis (6), and Kali carbonicum (4). (Table 3) When asked to rate the degree of confidence in their homeopathic prescriptions, the practitioners' responses were good (53.5%), fair (29.6%), excellent (16.1%), and poor (0.8%). When asked to predict at each visit to which treatment group each patient was assigned, there was no correlation between the actual treatment groups and the prediction. The most common response to which treatment group a given patient was assigned was "don't know" (200 of 367 visits). Homeopathic practitioners expressed frustration with the three arm design of the study,

stating that treatment decisions were difficult not knowing whether to prescribe as if the subject was receiving a daily combination medicine or an infrequent single remedy.

Univariate analysis

There was no significant difference in the hot flash severity score or total hot flashes between the three groups in the univariate model adjusted for baseline and time. (Table 3) However, the single remedy group had a lower severity score and fewer hot flashes in the group as a whole, which was most marked during the first three months of the study, with a positive trend (P=0.1) at three months when compared to placebo. (Figure 1)

Because tamoxifen is known to increase the number and severity of hot flashes, a subgroup analysis by use or non-use of tamoxifen was done. In this analysis, we found a statistically significant increase in the hot flash severity score in the combination homeopathy group when compared to placebo (p=0.01) and a highly significant difference when compared to single homeopathic remedy (p<0.001) in the group not receiving tamoxifen. (Table 3) Similarly, there was a highly significant increase in the total number of hot flashes in the combination group when compared to placebo (p=0.006) and compared to single remedy (p=0.002) in the group not receiving tamoxifen. This also can be seen in the time plot of the severity score of the no tamoxifen subgroup. (Figure 2) In the group that received tamoxifen, the combination group had a lower severity score and fewer hot flashes than those receiving the single remedy, although this was not significant.

There was a positive trend toward a lower Kupperman Menopausal Index score in the single remedy group compared to placebo in all subjects.(p=0.1). This difference translates to a 1.6 point decrease for each month longer a woman stayed in the study. There were no differences between the three groups in individual symptoms of the KMI except for a statistically significant increase in headaches in the group receiving the homeopathic combination at 6 months (p=0.04) and 12 months (p=0.03). A comparison of quality of life scores using the SF-36 found no significant differences, except in 1 of the 8 subscores, General Health (GH), which was significantly increased in both homeopathy groups when compared to placebo (p=0.02 single vs. placebo, p=0.03 combination vs placebo). (Figure 3). There was also a statistically significant incidence of reported side effects in the groups receiving placebo, compared to the two homeopathic treatment groups (p=0.002). There were no differences in FSH levels before or after treatment, although less than half of study subjects completed both measurements. Compliance was similar between all three treatment groups as assessed by questionnaire.

Multivariate analysis and sample size determination

In the multivariate analysis, which included baseline values, time, age, last month in the study, and treatment group, the same statistically significant relationships between treatment group and tamoxifen/no tamoxifen were found for both severity score and total number of hot flashes. Similarly, in the same model, the positive trend of the KMI score and the statistically significant differences in the GH score were found. Using the difference in the hot flash severity score between the single remedy group and placebo after six months, the sample size needed to show a positive treatment association with a power of 80% and an alpha of 0.05 would be 250 in each treatment group.

## DISCUSSION

The small sample size of this study precludes any definitive conclusions, but several observations can be made. While there was a positive trend towards a decreased hot flash severity score in the single remedy group during the first three months of the study, no significant differences between groups were found for the entire study period. (Figure 1) This could be due to the cumulative effect of tamoxifen in the single remedy group, along with regression to the mean in the placebo group. It is interesting to note that the hot flash severity score in the single remedy group does not increase over time in the no tamoxifen group. (Figure 2)

In the subjects not receiving tamoxifen, the statistically significant increase in both the hot flash severity score and the total number of hot flashes in the combination remedy group was striking and suggests that the effect of homeopathy is different than that of placebo. This increase could be explained by the phenomenon of the homeopathic "proving," which, according to the homeopathic literature, can occur when a homeopathic medicine is given frequently in low doses over time, that is, it will act paradoxically to cause a symptom it is meant to cure. In the experimental design of this trial, women were told to take the combination medicine in a controlled dose of three times daily for the course of the study. This is in contrast to the over-the-counter printed instructions for this preparation, which are to take until symptoms subside or to discontinue after seven days if symptoms worsen. This possibility is strengthened by the finding of increased headaches in the combination group, since all three medicines in the homeopathic combination (*Amyl nitrate, Lachesis,* and *Sanguinaria)* are associated with headaches.

In the subjects who did receive tamoxifen, there was no statistical difference in severity score or total number of hot flashes between the three groups, although in this subgroup, the combination group has lower scores. While tamoxifen did appear to increase the severity score and number of hot flashes in the single remedy and placebo groups, it did not seem to cause an increase in those receiving the combination medication. The reason for this is unknown, but one could speculate that that the effect of the homeopathic proving was comparable to that of tamoxifen, or that the effects of the two medicines was not additive. Since more than half of all subjects received tamoxifen, the difference in severity scores for the entire group was not significant.

Another interesting finding was the statistically significant improvement in General Health scores on the SF-36 quality of life index between both homeopathic groups and placebo. This should be interpreted with caution, as there were multiple comparisons made with the SF-36 and this was the only significant finding. However, an improvement in general health with homeopathy is consistent with the premise that homeopathy treats the whole person rather than acts on specific symptoms of disease. This finding is strengthened by the positive trend towards a lower Kupperman score in all subjects. These improvements did not appear to be affected by the use of tamoxifen, nor by the proving effect of the combination remedy, suggesting that general health was perceived independently from the number and severity of hot flashes

A curious finding was the statistically significant increased report of side effects, such as nausea and bloating, in the placebo group, including the one subject that withdrew due to adverse effects who was taking placebo. This could be due to artifact. An alternate explanation is that these could have been unrelated symptoms and that the homeopathic treatments prevented their

occurrence. The lack of difference in FSH levels between the groups is difficult to interpret, given the high use of tamoxifen and the small number of subjects obtaining these measurements.

Study limitations

As was previously stated, the major limitation is that of small sample size, which was not adequate to make meaningful conclusions. There were several additional limitations that could be addressed in a larger study. Difficulty in recruiting subjects and maintaining ongoing follow-up visits for one year was a major problem, since fully one-third of the subjects dropped out by the end of the study period. This could be mitigated by shortening the length of the study to six months, offering economic incentives for participation and completion of the study, and/or giving subjects the opportunity to receive what is known to be homeopathic verum medication after the study concludes. The use of three arms in this study made treatment decisions by the homeopathic practitioners difficult. An alternative protocol comparing the homeopathic combination to placebo (without the need for homeopathic practitioners) in one arm and the classical homeopathic treatment with placebo in a separate arm should be considered in future studies.

A major limitation was the use of the homeopathic combination medicine in an ongoing daily regimen, rather than as it is used in current over-the-counter treatment. While this prevented us from fully evaluating the utility of the combination medication for hot flashes, the improved general health in this group suggests that further studies should be carried out using the homeopathic combination medicine in a more appropriate manner. The statistically significant increase in hot flash severity and number that inadvertently occurred in the combination group suggests that homeopathic medications do have an effect that is different than placebo and provides experiment data consistent with the theoretical construct of the homeopathic "proving."

The use of tamoxifen, which causes hot flashes, by the majority of subjects in this study likely prevented the finding of more significant results, which has been found in other studies of hot flashes in breast cancer survivors. However, the large number of women taking this medicine (or newer estrogen inhibitors) precludes a study in breast cancer survivors that does not include tamoxifen. Furthermore, since this problem is an important one for breast cancer survivors, a treatment that is effective in reducing hot flashes even in those taking tamoxifen would be of great value. Our preliminary findings suggest this might be possible with homeopathy and further studies with larger sample sizes seems justified.

This study suggests that homeopathic medications, both single and in combination, may be effective in improving general health in breast cancer survivors. It also suggests that single remedy homeopathy may be effective in reducing the number and severity of hot flashes. In addition, the results suggest that homeopathy could be of value to the larger population of women who are not breast cancer survivors, but who want to avoid hormone replacement due to increased risk of breast cancer and other diseases. Future studies also should include health post-menopausal women to better understand the value of this treatment in those not taking tamoxifen or other estrogen inhibitors. Larger sample sizes should be utilized to increase statistical power and the study period should be shortened to no longer than six months.

Table 1. Withdrawal of subjects by treatment group

| | Combination (n=30) | Single remedy (n=26) | Placebo (n=27) | Total (n=83) |
|---|---|---|---|---|
| No relief hot flashes | 4 | 3 | 4 | 11 |
| Study inconvenient | 1 | 1 | 3 | 5 |
| Cancer recurrence | 3 | 0 | 1 | 4 |
| Lost to follow-up | 1 | 2 | 1 | 4 |
| Other illness | 2 | 0 | 1 | 3 |
| Adverse effect | 0 | 0 | 1 | 1 |
| Total withdrawn (12 mo) | 11 | 6 | 11 | 28 |
| Total withdrawn (6 mo) | 7 | 3 | 7 | 17 |

Table 2. Comparison of demographic factors and breast cancer staging and treatments between the three groups, (%).

| | Combination (n=30) | Single remedy (n=26) | Placebo (n=27) | P-value |
|---|---|---|---|---|
| Age (mean) | 55.4 | 56.8 | 54.5 | 0.62 |
| Race- white | 26 (87) | 26 (100) | 26 (96) | 0.57 |
| Married | 19 (63) | 18 (69) | 17 (63) | 0.80 |
| College graduate | 15 (50) | 16 (62) | 16 (59) | 0.67 |
| Income < $75,000* | 20 (77) | 18 (78) | 16 (72) | 0.91 |
| Currently employed | 21 (70) | 13 (50) | 14 (52) | 0.22 |
| Stage I or less at Diagnosis | 17 (57) | 16 (62) | 16 (59) | 0.82 |
| Mastectomy | 11 (37) | 12 (46) | 14 (52) | 0.71 |
| Chemotherapy | 18 (60) | 13 (50) | 14 (52) | 0.62 |
| Radiation | 23 (77) | 15 (58) | 19 (70) | 0.34 |
| Hormone Rx | 19 (63) | 16 (62) | 19 (70) | 0.75 |
| Tamoxifen | 16 (53) | 15 (58) | 17 (63) | 0.78 |

*(n=71)

Table 3. Univariate model of severity score and total number of hot flashes adjusted for baseline and time (continuous) by tamoxifen group and for all adjusted for baseline, time, and tamoxifen

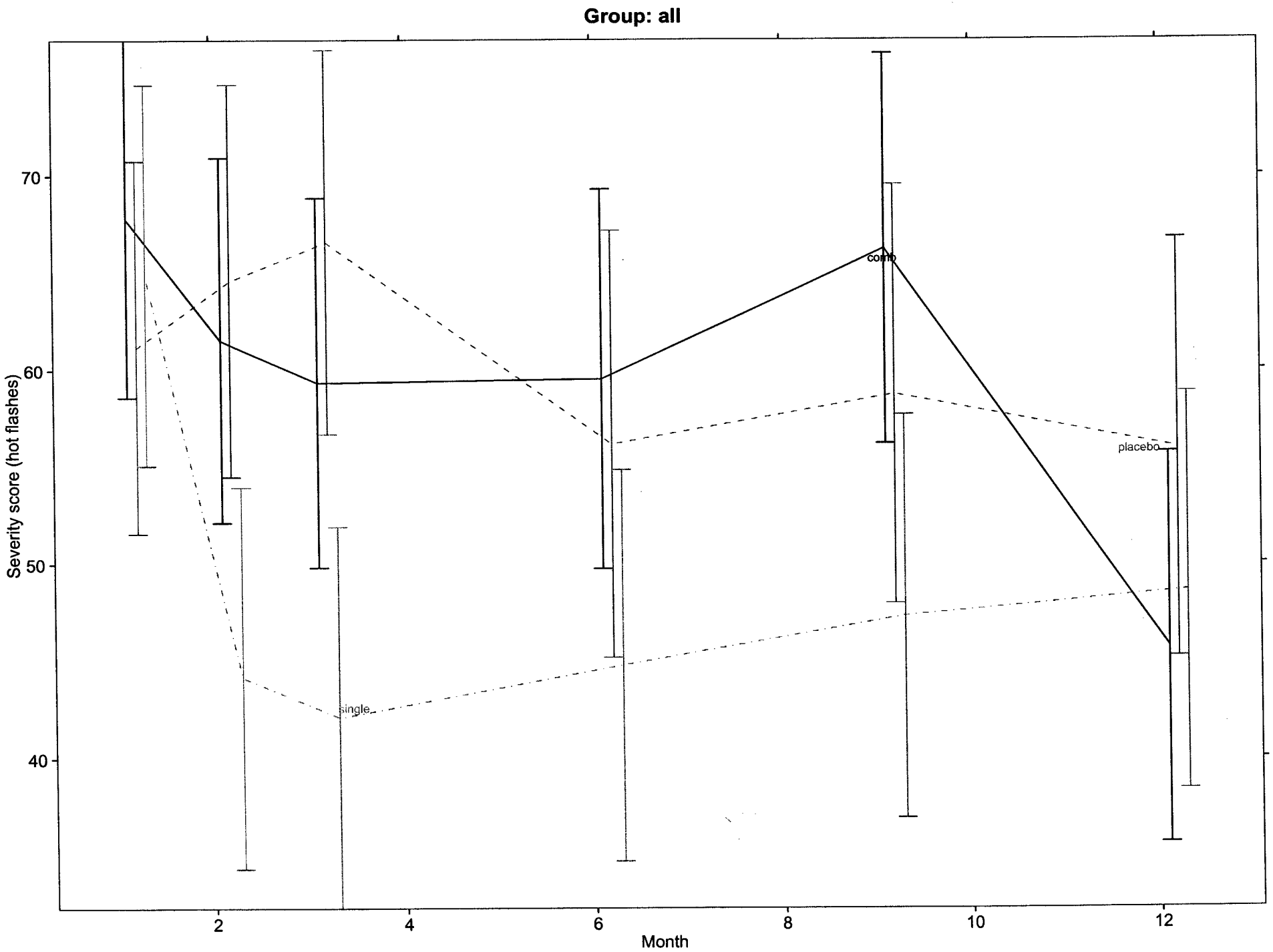
| | Value | SEM | p-value | 95% CI | |
|---|---|---|---|---|---|
| Severity score | | | | | |
| Tamoxifen | | | | | |
| Single vs Placebo | -6.5 | 17.9 | 0.7 | -41.6 | 28.6 |
| Comb vs Placebo | -13.3 | 17.5 | 0.4 | -47.5 | 20.9 |
| Comb vs Single | -6.8 | 18.3 | 0.7 | -29.1 | 42.7 |
| No Tamoxifen | | | | | |
| Single vs Placebo | -6.8 | 10.4 | 0.5 | -27.1 | 13.6 |
| Comb vs Placebo | 26.7 | 10.4 | **0.01** | 6.2 | 47.1 |
| Comb vs Single | 33.5 | 9.4 | **<0.001** | -51.9 | -15.0 |
| All | | | | | |
| Single vs Placebo | -12.0 | 11.4 | 0.3 | -34.3 | 10.3 |
| Comb vs Placebo | -0.4 | 11.2 | 1.0 | -22.3 | 10.3 |
| Comb vs Single | 11.6 | 11.1 | 0.3 | -33.4 | 10.2 |
| Total number of hot flashes | | | | | |
| Tamoxifen | | | | | |
| Single vs Placebo | -1.2 | 7.6 | 0.9 | -16.0 | 13.7 |
| Comb vs Placebo | -7.8 | 7.4 | 0.3 | -22.3 | 6.8 |
| Comb vs Single | -6.6 | 7.8 | 0.4 | -8.8 | 22.0 |
| No Tamoxifen | | | | | |
| Single vs Placebo | -0.3 | 6.3 | 1.0 | -12.7 | 2.1 |
| Comb vs Placebo | 17.7 | 6.4 | **0.006** | 5.2 | 30.2 |
| Comb vs Single | 18.0 | 5.9 | **0.002** | -29.5 | -6.5 |
| All | | | | | |
| Single vs Placebo | -2.5 | 5.3 | 0.6 | -12.9 | 8.0 |
| Comb vs Placebo | 2.2 | 5.3 | 0.7 | -8.1 | 12.6 |
| Comb vs Single | 4.7 | 5.3 | 0.4 | -15.1 | 5.7 |

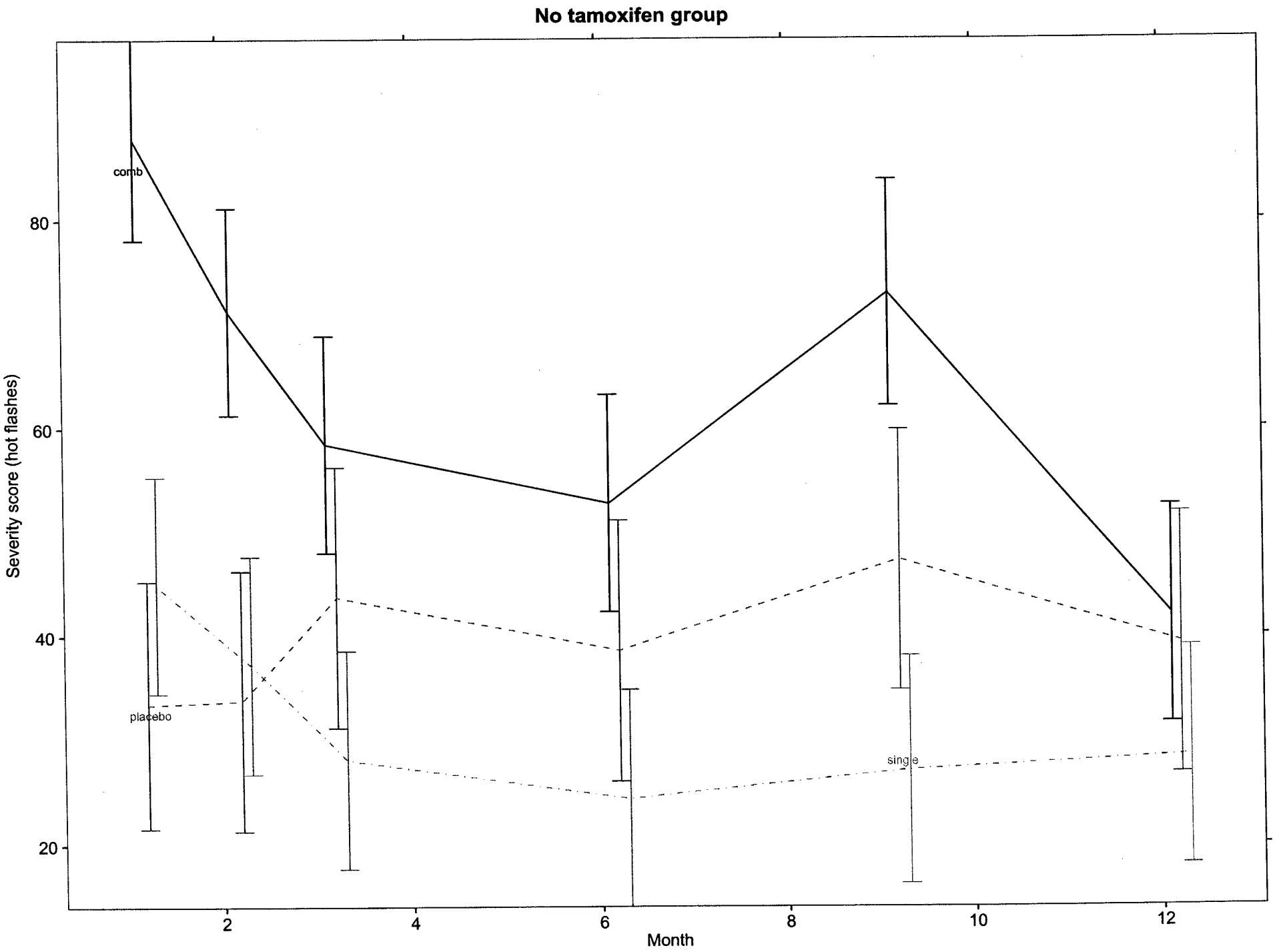
LEGENDS FOR FIGURES

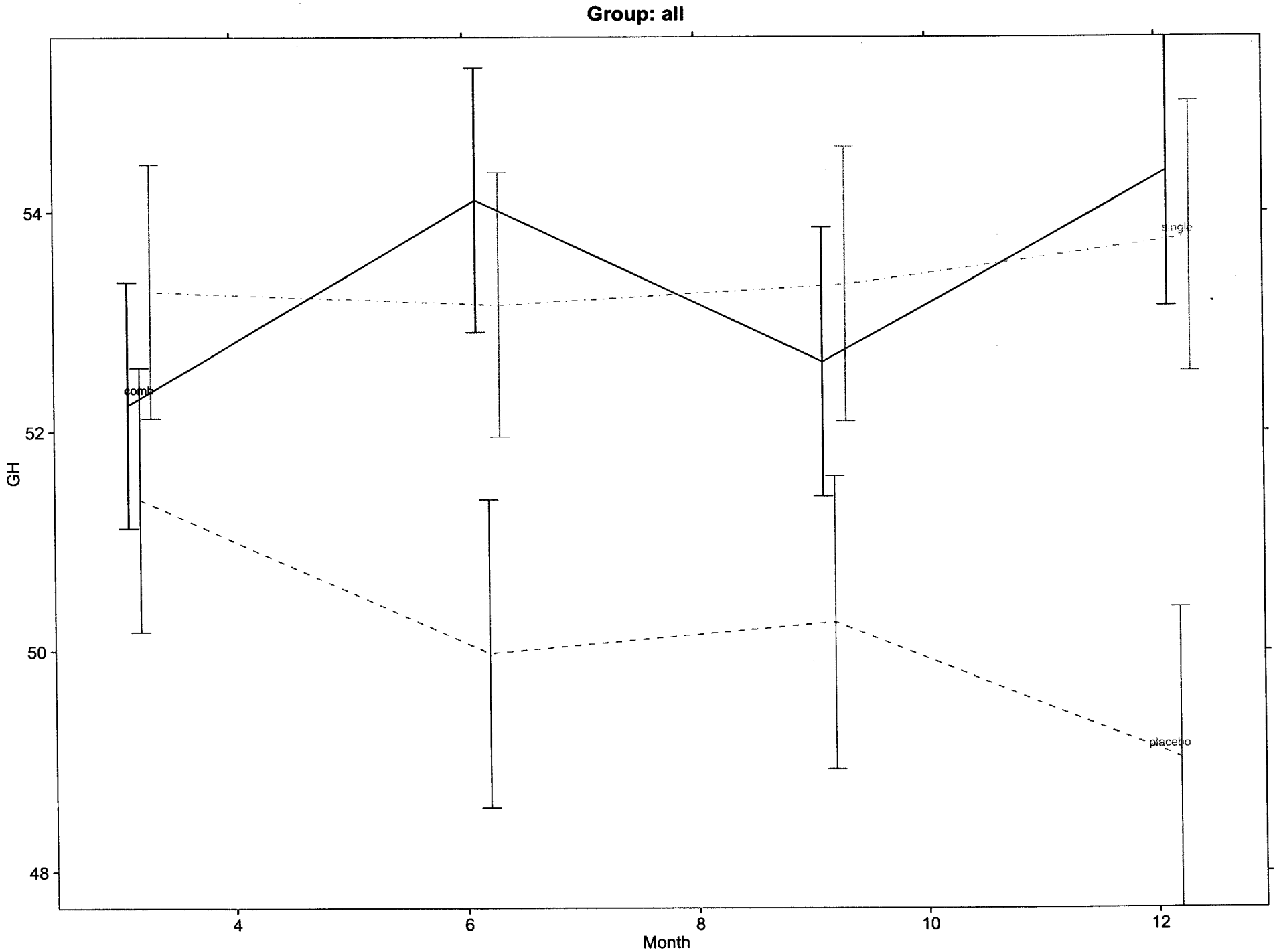
Figure 1. Time plot of hot flash severity score with standard deviations, all subjects.

Figure 2. Time plot of hot flash severity score with standard deviations, subjects not receiving tamoxifen

Figure 3. Time plot of General Health (GH) with standard deviations, all subjects


Group: all
Severity score (hot flashes)
70
60
50
40
2
4
6
8
10
12
Month
combo
placebo
single


No tamoxifen group
comb
placebo
single
Severity score (hot flashes)
80
60
40
20
2
4
6
8
10
12
Month


Group: all
GH
54
52
50
48
4
6
8
10
12
Month
comb
single
placebo

# APPENDIX 4- POWERPOINT PRESENTATION

## Homeopathy for Hot Flashes in Breast CA Survivors- a Pilot Study

Jennifer Jacobs, MD, MPH
University of Washington
Patricia Herman, PhD
Bastyr University

## Purposes of Pilot Study

- Determine methods of recruitment
- Test study design, protocol, and outcome instruments
- Determine whether there is a positive trend in reduction of symptoms with homeopathy
- Estimate sample sizes required in a full-scale trial

## Patient Eligibility

- History of Carcinoma-in-Situ or Stages 1-3 Breast CA
- Completed all surgery, chemotherapy, and radiation treatments
- Hot flashes- average 3/day for one month prior to enrollment
- Women on Tamoxifen therapy included

## Patient Exclusions

- Concurrent chronic health problems requiring treatment with steroids
- Taking other meds for hot flashes-
  - Vitamins, herbs
  - Estrogen, progesterone agents
  - Anti-depressants/sleep meds
- Expected to receive chemo or radiation or to become pregnant within the next year

## Study design

- All patients interviewed by experienced homeopathic provider (>10 years experience)
- Patients randomized to one of three arms:
  - Homeopathic combination- *Hyland's Menopause*
    Amyl nitrate 3X, Sanguinaria 3X, Lachesis 12X
    One dose 3 times daily
  - Single individualized homeopathic remedy
    Variable dosage schedule
  - Placebo

## Study design-2

- Medications sent by express mail-
  double dummy design:
  - Group A — Verum combination; Placebo single remedy
  - Group B — Placebo combination; Verum single remedy
  - Group C — Placebo combination; Placebo single remedy

## Follow-up visits

- Homeopathic- 2, 4, 6, 8, 10, 12 months
  - Change remedy at any time
  - Prescribe any remedy, potency or frequency
- Telephone interview/study diary- 1, 2, 3, 6, 9, 12 months
  - Hot flash diary- frequency and severity
  - Kupperman Menopausal Index- common sxs
  - SF-36 Quality of Life- physical, mental scores

## Outcomes

- Hot flash score- frequency X severity
- Total # hot flashes
- Kupperman Menopausal Index- weighted score

| | | | |
|---|---|---|---|
| Hot flashes | 4 | Depression | 1 |
| Numbness/tingling | 2 | Dizziness | 1 |
| Insomnia | 2 | Fatigue | 1 |
| Nervousness | 2 | Muscle/joint pain | 1 |
| Headaches | 1 | Palpitations | 1 |
| Itching | 1 | | |

## Outcomes- Quality of Life

- SF-36 Quality of Life Score- 8 subscores
  - Mental composite score
    - Vitality, Social function, Role emotional, Mental health
  - Physical composite score
    - General health, Bodily pain, Role physical, Physical function

## Outcomes-Cost Effectiveness

- Quality-Adjusted Life-Years (QALYS)
  - Estimated using model from SF-36 (Brazier)
  - Based on specific questions from SF-36
  - Score from 0 (death) to 1 (perfect health)

## Outcomes- Cost effectiveness

- Total cost of health care for study year
  - Chart review of all medical visits, n=47
  - Cost of homeopathic intervention
    - Combination- $8 X 12 months = $96
    - Single- $300 first visit + $75 X 5= $675

## Recruitment and Withdrawals

- 83 women interviewed and randomized
- 17 total withdrawals (19.5%)- 6 mos
- 28 total withdrawals (33.7%)- 12 mos

  11 each combination/placebo, 6 single remedy
  - 11 No relief from hot flashes
  - 7 Cancer recurrence (4) or other illness
  - 5 Study inconvenient
  - 4 Lost to follow-up
  - 1 Adverse effect

## Remedies Prescribed

- 35 different remedies prescribed 1st visit
- 12 most common remedies prescribed:

| | |
|---|---|
| Sepia | 9 |
| Calcarea carb | 8 |
| Sulphur | 6 |
| Lachesis | 6 |
| Kali-carb | 4 |
| Arg-nit, Ars-alb, Carcinosin | 3 |
| Nat-mur, Phos, Silica, Thuja | 3 |

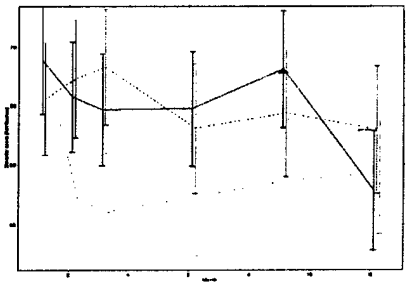
## Homeopathic Provider Evaluations

- Confidence in remedy prescribed- all visits
  - Excellent 16.1%
  - Good 53.5%
  - Fair 29.9%
  - Poor 0.8%
- No correlation between prediction of and actual treatment group
- Reported frustration with 3-arm design- difficult to make treatment decisions

## Results- Hot Flash Severity Score

- All subjects- hot flash severity score
  - Single remedy dropped in first 2-3 mos, positive trend p=0.1 compared to placebo
  - No other significant differences in model with baseline values and dropouts

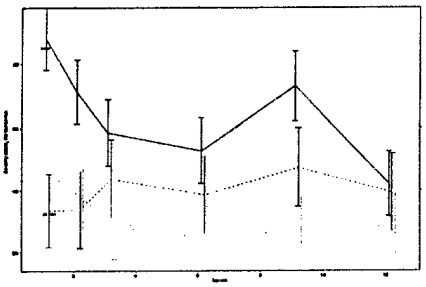
## Hot Flash Severity - all subjects



## Results- Hot Flash Severity Score

- No Tamoxifen-
  - Single vs Placebo- no significant difference
  - Combination vs Placebo- significant increase in combination group, p=0.01 over entire time
  - Combination vs Single- highly significant increase in combination group, p<0.001 over entire time

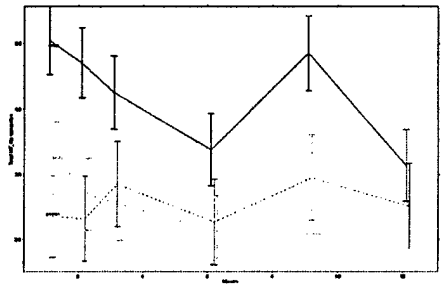
## Hot flash severity- No Tamoxifen



## Total Hot Flashes

- All patients- Drop in single in first 2-3 months, no significant differences
- No Tamoxifen group
  - Single vs Placebo- no significant difference
  - Combination vs Placebo- highly significant increase in combination group, p=0.006
  - Combination vs Single- highly significant increase in combination group, p=0.002

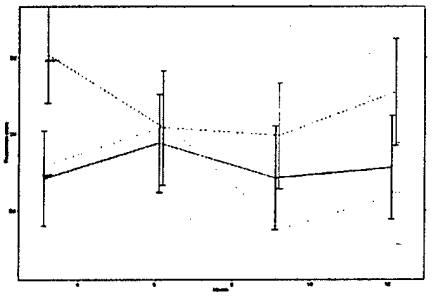
## Total Hot flashes- No Tamoxifen



## Results- Kupperman Index

- Linear decrease over time for total score in single remedy group, p=0.1 at 12 mos
- Statistically significant increase in headaches in combination group
  - 6 months- p=0.04
  - .12 months- p=0.03
- No other significant differences found

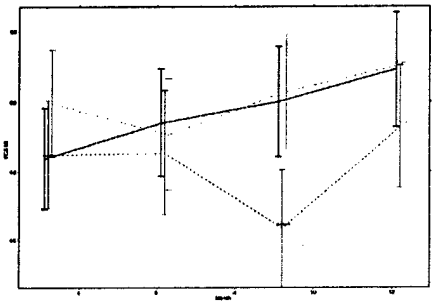
## Kupperman Score- all subjects



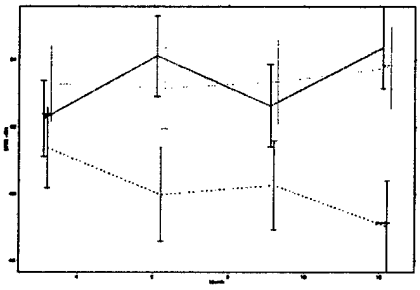
## Results- SF-36 Quality of Life

- Physical Composite Score
  - Positive trend over placebo in both single remedy and combination groups
- General Health Score
  - Improved significantly over placebo in both single remedy and combination groups, p=0.03
- No other significant differences found

## Physical Composite Score



## General Health Score- all subjects



## Average Costs and Changes in Quality-Adjusted Life Years

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## Cost-Effectiveness Ratios

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## Study Limitations

- One year study period resulted in large drop-out rate (33.7%)
- Difficult to recruit women to study with chance of placebo for one year
- Three-arm study design complicated homeopathic treatment decisions
- Use of Tamoxifen high in Breast CA survivors, strong anti-estrogenic effect

## Preliminary Conclusions- 1

- The single remedy produced a decrease in hot flash frequency and severity that was most marked in the first three months
- Daily dose of combination appears to have caused proving symptoms
  - Increased severity and # of hot flashes- more evident without Tamoxifen
  - Increased headaches on Kupperman score

## Preliminary Conclusions- 2

- Single and combination homeopathy appear to improve general health and physical functioning on the SF-36
- Combination homeopathy may be more cost effective than single remedy

## Future Recommendations

- Shorten study period to 6 months
- Randomize to single or combination, then to verum or placebo in each arm
- Change dosage of combination to as needed, not three times daily
- Consider expanding study to include non-Breast CA subjects- no Tamoxifen